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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/787,327 | 04/20/2001 | Nathaniel A. Brown | PU3514USW | 9628 |

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EXAMINER

JIANG, SHAOJIA A

ART UNIT PAPER NUMBER

1617

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 09/787,327 | BROWN ET AL. | |
| | Examiner | Art Unit | |
| | Shaojia A Jiang | 1617 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 December 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4-9, 15 and 24 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4-9, 15 and 24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office Action is a response to Applicant's amendment and response filed on December 16, 2003 wherein claims 1-3, 10-14, and 16-23 are cancelled, and Claims 4-9 and 15 have been amended; Claim 24 is newly submitted.

Currently, claims 4-9, 15 and 24 are pending in this application.

Claims 4-9, 15 and 24 as amended now are examined on the merits herein.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 4-9, 15 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shaw et al. (of record) and Korba (of record) in view of Glazier et al. (5,627,165, of record) for the same reasons of record in the previous Office Action June 18, 2003.

Shaw et al. discloses that a combination of lamivudine (also known as 3TC whose chemical name is the first compound recited in claim 5 herein) and PMEA (also known as adefovir) exhibits a synergistic inhibition of HBV. Shaw et al. also discloses the effective amount of PMEA ($0.15/5 \mu\text{M} = 0.03 \mu\text{M}$, since it reduced 5 fold in the

presence of 0.05 μ M 3TC in the combination to be administered simultaneously (see the abstract). Hence, the ratio of 3TC to PEMA is 1.67:1, within the instant claimed range.

Korba teaches lamivudine is useful in methods of treatment of HBV infections. Korba also teaches that lamivudine in combination with other antiviral agents such as penciclovir which is known antiviral agent against HBV is useful in a pharmaceutical composition or formulation for oral administration and methods of treatment of HBV infections, exhibiting synergistic effect. See abstract, the right column of page 49, the 3rd and 4th paragraphs of page 50.

The prior art does also not expressly disclose a pharmaceutical composition or formulation comprising lamivudine (3TC) and adefovir dipivoxil, the prodrug of PEMA in unit dosage form and the particular ratio of lamivudine (3TC) and the prodrug of PEMA herein, the manner of administration of the pharmaceutical composition or formulation herein.

Glazier et al. discloses that adefovir (PMEA) or adefovir dipivoxil (Bis(pivaloyloxymethyl)PMEA, the prodrug of PMEA herein whose chemical name is the second compound recited in claim 5 herein) is known to be useful in a pharmaceutical composition or formulation and methods of treatment of HBV infections. Glazier et al. also discloses that the prodrug of PMEA herein enhances intracellular PMEA delivery and have enhanced antiviral activity (see particularly col.1 lines 66 to col.2 line 2, col.3-6). See also col.34 lines 39-40, col.37 lines 5-19, col.38 Tables, and claims 1-38.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ lamivudine in combination with adefovir dipivoxil, the

prodrug of PMEA herein, in a pharmaceutical composition or formulation and methods of treatment of HBV infections, and to determine the manner of administration of the pharmaceutical composition or formulation herein and to optimize the effective amounts of active agents in the composition herein to be administered.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ lamivudine in combination with adefovir dipivoxil, the prodrug of PMEA herein, in a pharmaceutical composition or formulation and methods of treatment of HBV infections, since the combination of lamivudine (3TC) and PMEA (adefovir) is known to be useful in a pharmaceutical composition or formulation and in methods of treatment HBV infections because the combination of lamivudine (3TC) and adefovir is known to exhibit synergistic effects against HBV according to Shaw et al. Moreover, adefovir dipivoxil, the prodrug of PMEA herein is known to be better than the parent drug, PMEA, since the prodrug of PMEA herein is known to enhance intracellular PMEA delivery and have enhanced antiviral activity according to Glazier et al. Therefore, one of ordinary skill in the art would have found it obvious to employ the prodrug of PMEA in combination with lamivudine (3TC) based on the prior art teachings. Hence, the disclosure of Shaw et al. has clearly provided the motivation of making the combination herein in view of Glazier et al.

Further, one of ordinary skill in the art would have reasonably expected that combining lamivudine and adefovir or adefovir dipivoxil known useful for the same purpose in a composition to be administered would improve the therapeutic effect for treating HBV infections.

Since all composition components herein are known, it is considered prima facie obvious to combine them into a single composition useful for the very same purpose. At least additive therapeutic effects would have been reasonably expected. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980).

Additionally, one of ordinary skill in the art would have been motivated to determine the manner of administration of the composition herein and to optimize the effective amounts of active ingredients in the composition because the determination of the manner of administration and the optimization of amounts of active agents to be administered is considered well within the skill of artisan. It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients and the manner of administration, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Argument

Applicant's remarks filed on December 16, 2003 with respect to the rejection of claims 1-2, 4-10, 12-15, and 22-23 made under 35 U.S.C. 103(a) as being unpatentable over Shaw et al. and Korba in view of Glazier et al. (5,627,165) of record in the previous Office Action June 18, 2003 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

Applicant argument that neither Shaw, nor Korba or Glazier disclose the therapeutically-effective ratio of lamivudine (also known as 3TC) and adefovir dipivoxil which is the prodrug of adefovir (known as the prodrug of PMEA) is not convincing since the ratio of lamivudine (3TC) to PEMA, 1.67:1 (within the claimed range) is known according Shaw. Adefovir dipivoxil, the prodrug of PMEA herein is known to not only have the same therapeutic usefulness but also better than the parent drug, PMEA, since the prodrug of PMEA herein is known to enhance intracellular PMEA delivery and have enhanced antiviral activity according Glazier et al. Thus, one of ordinary skill in the art would use the same or similar ratio of lamivudine (3TC) to PEMA in the ratio of lamivudine (3TC) and the prodrug of PMEA, or optimize the ratio, as the court states that "The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages" (see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382). Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical, as noted MPEP 2144.04.

Applicant also argues that the cited prior art does not disclose the treatment of resistant HBV. However, one of ordinary skill in the art would have reasonably expected that the combination herein would also have beneficial therapeutic effects and usefulness in methods of the treatment of resistant HBV based on the prior art teachings for treating HBV.

Applicant's assertion that Figure 1 of the specification demonstrates the claimed combination herein shows unexpected and synergistic activity against HBV production has been considered but is not found convincing since the synergistic results in the testing of the combination of lamivudine and PMEA (adefovir) shown in Figure 1 in the specification is clearly taught and suggested by Shaw et al. Therefore, the results herein are clearly expected and not unexpected based on the cited prior art. It is noted that the combination tested herein is not the combination of lamivudine and the prodrug of PMEA, adefovir dipivoxil as instantly claimed. Nonetheless, the combination of lamivudine and adefovir dipivoxil (the prodrug of PMEA) would be also expected to show synergistic effects against HBV and resistant HBV based on the prior art. Expected beneficial results are evidence of obviousness. See MPEP § 716.02(c).

Therefore, the evidence presented in the specification herein is not seen to support the nonobviousness of the instant claimed invention over the prior art.

In view of the rejections to the pending claims set forth above, no claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

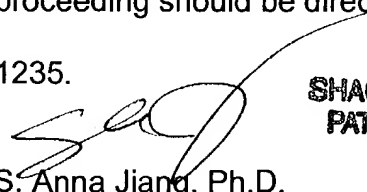
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.


S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
April 14, 2004

SHAOJIA ANNA JIANG
PATENT EXAMINER